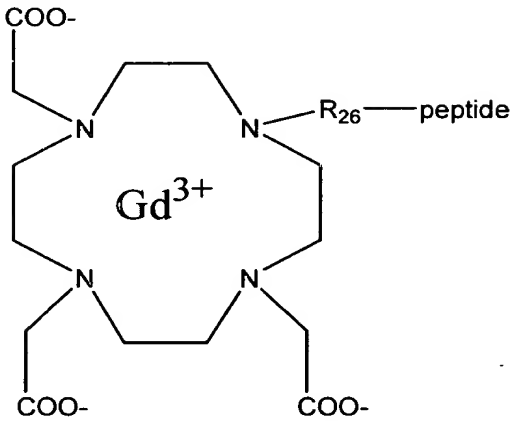
12. (Amended) An MRI agent having the formula:



wherein R_{26} is a linker.

16. (Twice Amended) An MRI agent according to claim 12 wherein R_{26} comprises -$(CH_2)CO)$-.

REMARKS

Claims 12, 16, 17, and 22-23 are pending. Claims 2-5, 8-11, 13-15, and 18-21 have been cancelled as being drawn to a non-elected invention/species. An Appendix of Pending claims is attached for the Examiner's convenience.

Rejection under 35. U.S.C. § 112, second paragraph:

Claims 11, 12 ,16-19, 22, and 23 are rejected under 35. U.S.C. § 112, second paragraph for being indefinite. Claim 12 has been rewritten as an independent claim from which claims 16, 17, 22 and 23 depend. Accordingly, Applicants request withdrawal of the rejection.

Obviousness-Type Double Patenting Rejection:

Claims 2, 11, 16-19, 22 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 9, 11, 14, and 16 of U.S. Patent No. 5,707,605.

Claims 2, 11, 12, 16-19, 22, and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 9. 29, and 30 of U.S. Patent No. 5,980,862.

Applicants request that this issue be held in abeyance until otherwise allowable subject matter is found, at which point a terminal disclaimer may be filed.

Rejection Under 35 U.S.C. § 103(a):

Claims 2, 11, 12, 16, 17, 22, and 23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Garlich *et al.* (US Patent Number 5,133,956) in view of Watson (US Patent No. 5,914,095.)

The Examiner states that it would have been obvious to someone of skill in the art to combine the metal binding protein compositions disclosed by Garlich with the teachings of Watson to make the MRI agents of the present invention.

Applicants submit that Garlich *et al.*, combined with Watson does not disclose the same components as those claimed in the present invention. The present invention claims a composition comprising a chelator, a paramagnetic metal ion, and a blocking moiety. The "blocking moiety" component of the present invention is not the same as the protein components described in Garlich, *et al* or Watson. As defined in the specification at page 20, lines 7-16:

> By "blocking moiety" or grammatical equivalents herein is meant a functional group associated with the chelator metal ion complexes of the invention which is capable of interacting with a target substance and which is capable, under certain circumstances, of substantially blocking the exchange of water in at least one inner coordination site of the metal ion of the metal ion complex. For example, when bound to or associated with the metal ion complexes of the invention, the blocking moiety occupies or blocks at least one coordination site of the metal ion in the absence of the target substance. Thus, the metal ion is coordinately saturated with the chelator and the blocking moiety or moieties in the absence of the target substance.

As can be seen from the above definition, a blocking moiety is not the equivalent to the protein component of the metal binding protein compositions described by Garlich *et al.*, or the macromolecule component of the bifunctional chelates described by Watson. As set forth in the specification at page 20, the blocking moiety of the present invention must perform at least three functions. First, the therapeutic blocking moiety must be capable of inhibiting the exchange of water in at least one inner coordination site of the metal ion. Second, the therapeutic blocking moiety must be capable of effecting a therapeutic effect. Finally, the therapeutic blocking moiety must be capable of increasing the exchange of water

in at least one inner coordination site of the metal ion either as a result of the interaction of the therapeutic blocking moiety with a target or as the result of the action of a separate enzyme on a cleavage site present in the therapeutic blocking moiety.

To accomplish the above functions, the blocking moiety may comprise one or more components. As outlined in the specification at page 20, lines 17-26:

> A blocking moiety may comprise several components. The blocking moiety has a functional moiety which is capable of interacting with a target substance, as outlined below. This functional moiety may or may not provide the coordination atom(s) of the blocking moiety. In addition, blocking moieties may comprise one or more linker groups to allow for correct spacing and attachment of the components of the blocking moiety. Furthermore, in the embodiment where the functional group of the blocking moiety does not contribute a coordination atom, the blocking moiety may comprise a coordination site barrier, which serves to either provide a coordination site atom or sterically prevent the rapid exchange of water at the coordination site; i.e. the coordination site barrier may either occupy or block the coordination site.

As the choice of the blocking moiety is dependent of the target, the components of the blocking moiety may comprise a wide variety of agents, including proteins (see specification at page 21, lines 7-22). For example, if the target is an enzyme, one component of the blocking moiety may be an enzyme inhibitor (see specification at page 21, line 23 through page 22, line 2). In addition, the blocking moiety may comprise a linker (see specification at page 28, line 18 through page 29, line 18). The purpose of the linker is to optimize the interaction of the blocking moiety with the metal ion (see specification at page 28, lines 22-26).

Watson discloses bifunctional chelates that may comprise a protein. The protein component of Watson is not the equivalent of the blocking moiety of the present invention as it functions to concentrate the bifunctional chelates in a particular location (see Column 11, line 46 through Column 12, line 14). Thus, Watson does not teach blocking moieties having the same functions and components as described in the present invention.

Garlich *et al.*, teach a method of delivering radionuclides linked to a high molecular weight metal binding protein for use in radiation ablation procedures. The protein component is of Garlich *et al.*, inert and is selected for its ability to bind metal cations (see Column 2, lines 25-64) and for its ability to remain at the site of injection (see Column 2, lines 9-21).

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g.*, *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met. First, the prior art reference, or references when combined, must teach or suggest each and every limitation of the rejected claims. *See, e.g.*, M.P.E.P. § 706.02(j). Second, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would be successful. *See, e.g., In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of the reference in the manner suggested by the Examiner. *See, e.g., In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

As can be seen from the above discussion, neither Garlich *et al.*, or Watson teach each and every element of the present invention. Specifically, neither reference, alone or in combination teaches the use of an MRI agent comprising a blocking moiety attached to a chelate/paramagnetic ion complex.

Based on the teachings of Watson and Garlich *et al.*, a skilled artisan would have no reasonable expectation of success of making an MRI agent of the present invention. In particular, the present invention teaches magnetic resonance imaging (MRI) contrast agents that are relatively inactive, e.g. they are "off" until they interact with a target substance. As a result of the interaction between the target and the blocking moiety, the MRI agents are activated, e.g. they turn "on" and enhance the observed image. See specification at page 11, lines 6-10.

Lastly, there is no suggestion or motivation either in the references themselves or in the knowledge available to one of skill in the art to modify or combine the teachings of Garlich *et al.*, and Watson. The Office Action states it would have been obvious to one skilled in the art to modify the teaching of Garlich et al with Watson et al (page 7 line 3). However, this does not provide sufficient basis for combining the references.

> A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

MPEP 2143.01.

As stated above, neither reference teaches the use of a blocking moiety that functions as a trigger, whereby the contrast agent is "turned on" by the interaction of the blocking moiety with a target substance. Applicants respectfully request that the rejection of claims 2, 11, 12, 16, 17, 22 and 23 under § 103(a) be withdrawn.

Claims 2 and 11 have been withdrawn and are thus not at issue. The remainder of the Claims are dependent upon current independent Claim 12 which the applicants submit is nonobvious, thus, all Claims dependent on Claim 12 are also nonobvious. MPEP 2143.03 *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed.Cir. 1988).

Attached hereto is a marked-up version of the changes made to the claims by the "Restriction and Amendment". The attached page is captioned **"Version with markings to show changes made."**

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels that there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Dated: 11/12/01

Respectfully submitted,

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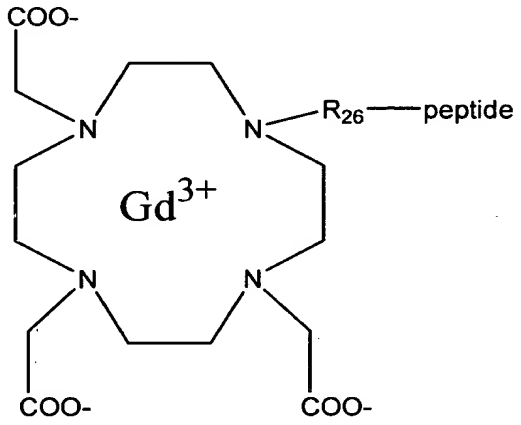
1061025.RMK

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the claims:

Claim 12 has been amended as follows:

12. (Amended) An MRI agent ~~according to claim 1~~ having the formula:



wherein R_{26} is a linker.

Claim 16 has been amended as follows:

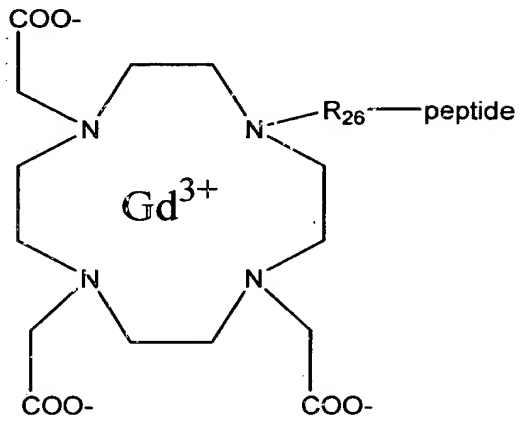
16. (Twice Amended) An MRI agent according to claim 12~~[, 13 or 14]~~ wherein R_{26} comprises $-(CH_2)CO-$.

Claim 20 has been cancelled.

Claim 21 has been cancelled.

Appendix of Pending Claims

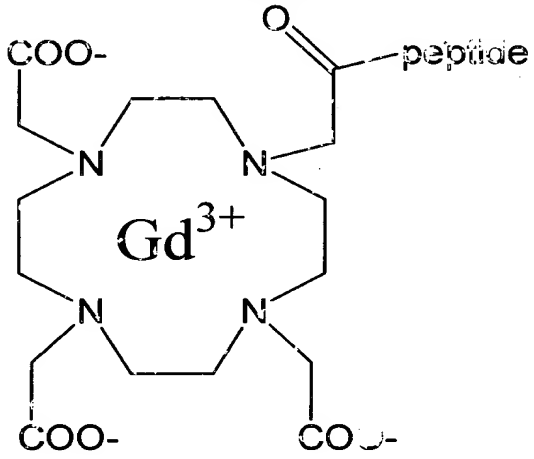
12. (Amended) An MRI agent having the formula:



wherein R_{26} is a linker.

16. (Twice Amended) An MRI agent according to claim 12 wherein R_{26} comprises -$(CH_2)CO)$-.

17. An MRI agent according to claim 16 having the formula:



22. An MRI agent according to claim 12 wherein said peptide inhibits a protease.

23. An MRI agent according to claim 22 wherein said protease is selected from the group consisting of caspase, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase.--